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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 January 2004 (15.01.2004)

PCT

(10) International Publication Number
WO 2004/005307 A1

(51) International Patent Classification[7]: C07H 9/04, C07D 333/20, 493/14 // (C07D 493/14, 319:00, 317:00, 317:00, 307:00)

(21) International Application Number: PCT/EP2003/007312

(22) International Filing Date: 8 July 2003 (08.07.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
02015161.9 9 July 2002 (09.07.2002) EP

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(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

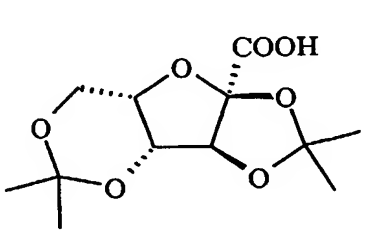
(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*
— *of inventorship (Rule 4.17(iv)) for US only*

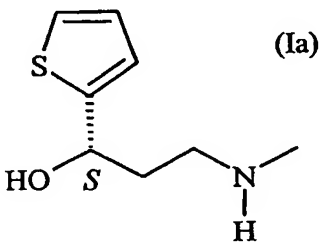
Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PROCESS FOR THE PREPARATION OF OPTICALLY ACTIVE 3-*N*-METHYLAMINO-1-(2-THIENYL)-1-PROPANOL



(IIa)



(Ia)

(57) Abstract: Enantiomerically enriched (*S*)-(-)-3-*N*-methylamino-1-(2-thienyl)-1-propanol or (*R*)-(+)-3-*N*-methylamino-1-(2-thienyl)-1-propanol of the formulae, or mirror image are prepared by i) treating an enantiomeric mixture of the amines Ia and Ib with (-)-2,3:4,6-di-*O*-isopropylidene-2-keto-L-gulonic acid or (+)-2,3:4,6-di-*O*-isopropylidene-2-keto-D-gulonic acid of the formulae (IIa) or mirror image ii) crystallizing the obtained diastereomerically enriched salts from the reaction mixture obtained in step i), iii) optionally recrystallizing said diastereomerically enriched salts IIIa or IVb, and iv) treating the diastereomerically enriched salts IIIa or IVb obtained in step ii) or step iii) with a base to liberate the enantiomerically enriched amines Ia or Ib.

WO 2004/005307 A1

Process for the preparation of optically active 3-*N*-methylamino-1-(2-thienyl)-1-propanol

The present invention refers to a process for the preparation of enantiomerically enriched (*S*)-(−)-3-*N*-methylamino-1-(2-thienyl)-1-propanol or (*R*)-(+)-3-*N*-methylamino-1-(2-thienyl)-1-propanol, to the salts of these amines with (−)-2,3:4,6-di-*O*-isopropylidene-2-keto-L-gulonic acid or (+)-2,3:4,6-di-*O*-isopropylidene-2-keto-D-gulonic acid, and to a process for the preparation of (*S*)-(+)-methyl-[3-(1-naphthyloxy)-3-(2-thienyl)-propyl]-amine (duloxetine) from an enantiomeric mixture of (*S*)-(−)-3-*N*-methylamino-1-(2-thienyl)-1-propanol and (*R*)-(+)-3-*N*-methylamino-1-(2-thienyl)-1-propanol.

(*S*)-(−)-3-*N*-Methylamino-1-(2-thienyl)-1-propanol is an intermediate for the preparation of (*S*)-(+)-methyl-[3-(1-naphthyloxy)-3-(2-thienyl)-propyl]-amine (duloxetine), an agent for the treatment of depression and urinary incontinence (Huiling et al. *Chirality* **2000**, *12*, 26-29, Sorbera et al. *Drugs of the Future* **2000**, *25(9)*, 907-916).

Huiling et al. (*Chirality* **2000**, *12*, 26-29) describe a preparation of (*S*)-(−)-3-*N*-methylamino-1-(2-thienyl)-1-propanol from thiophene. Thiophene was converted with 3-chloropropanoyl chloride in the presence of tin tetrachloride in benzene to 3-chloro-1-(2-thienyl)-1-propanone, which was reduced with sodium borohydride in ethanol to 3-chloro-1-(2-thienyl)-1-propanol. Kinetic resolution by transesterification using vinyl butanoate and lipase B from *Candida antarctica* as catalyst in hexane yielded (*S*)-3-chloro-1-(2-thienyl)-1-propanol, which was converted to (*S*)-3-iodo-1-(2-thienyl)-1-propanol using sodium iodide in acetone. Subsequent treatment with methylamine in tetrahydrofuran afforded (*S*)-(−)-3-*N*-methylamino-1-(2-thienyl)-1-propanol.

Sorbera et al. (*Drugs of the Future* **2000**, *25(9)*, 907-916) describe another preparation of (*S*)-(−)-3-*N*-methylamino-1-(2-thienyl)-1-propanol from thiophene, which is essentially the same as the one described by Huiling et al. (*Chirality* **2000**, *12*, 26-29) except that 3-chloro-1-(2-thienyl)-1-propanone was directly asymmetrically reduced to (*S*)-3-chloro-1-(2-thienyl)-1-propanol using borane and catalytic amounts of (*R*)-3,3-diphenyl-1-methyltetrahydro-3*H*-pyrrolo[1,2-c][1,3,2]oxazaborole in tetrahydrofuran. This asymmetric reduction afforded (*S*)-3-chloro-1-(2-thienyl)-1-propanol in a yield of 86%

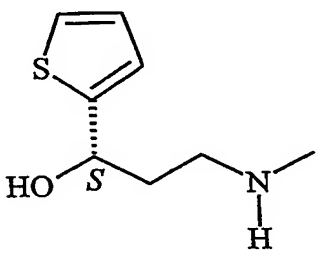
from 3-chloro-1-(2-thienyl)-1-propanone (Wheeler et al. *J. Label. Compd. Radiopharm.* 1995, *36*, 213-223).

The drawbacks of above preparations of (*S*)-(−)-3-*N*-methylamino-1-(2-thienyl)-1-propanol are the use of toxic or carcinogenic compounds such as tin tetrachloride and benzene and the use of expensive compounds such as borohydride or borane and sodium iodide, the latter being in addition difficult to dispose.

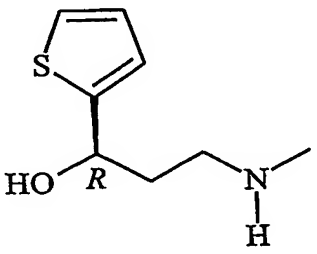
It is an object of the present invention to provide an ecological and economical process for the preparation of (*S*)-(−)-3-*N*-methylamino-1-(2-thienyl)-1-propanol or (*R*)-(+)-3-*N*-methylamino-1-(2-thienyl)-1-propanol. It is another object of the present invention to provide an ecological and economical process for the preparation of (*S*)-(+)-methyl-[3-(1-naphthyloxy)-3-(2-thienyl)-propyl]-amine (duloxetine) and to provide new amine addition salts of (−)-2,3:4,6-di-*O*-isopropylidene-2-keto-L-gulonic acid or (+)-2,3:4,6-di-*O*-isopropylidene-2-keto-D-gulonic acid.

These objects are achieved by the processes according to claims 1 and 10, and by the compounds according to claims 13 to 16.

The process of the present invention for the preparation of enantiomerically enriched (*S*)-(−)-3-*N*-methylamino-1-(2-thienyl)-1-propanol or (*R*)-(+)-3-*N*-methylamino-1-(2-thienyl)-1-propanol of the formulae



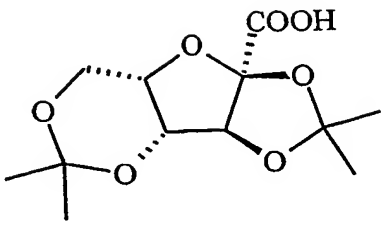
(Ia) or



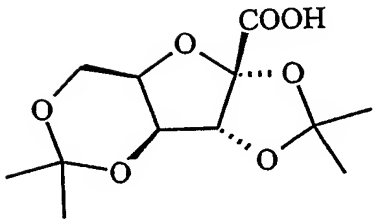
(Ib)

comprises the steps of

i) treating an enantiomeric mixture of the amines Ia and Ib with (−)-2,3:4,6-di-*O*-isopropylidene-2-keto-L-gulonic acid or (+)-2,3:4,6-di-*O*-isopropylidene-2-keto-D-gulonic acid of the formulae

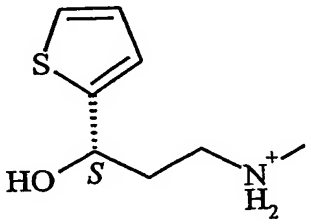


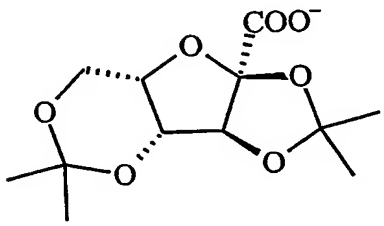
(IIa) or



(IIb)

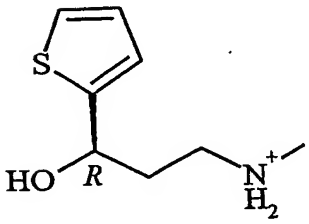
to partially or completely form the diastereomeric salts of the formulae

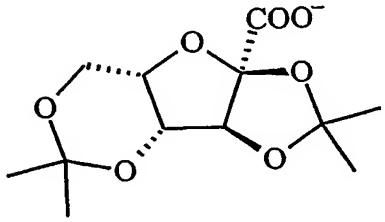




(IIIa)

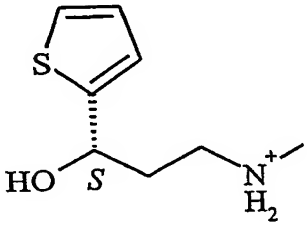
and

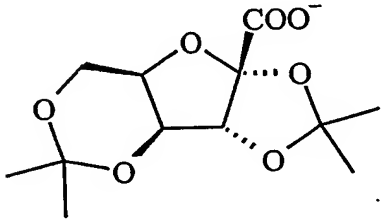




(IIIb)

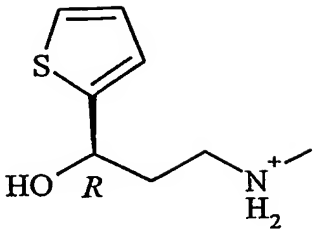
or the diastereomeric salts of the formulae

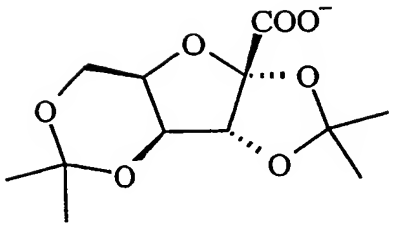




(IVa)

and





(IVb)

ii) crystallizing the diastereomerically enriched salts IIIa or IVb from the reaction mixture obtained in step i),

iii) optionally recrystallizing said diastereomerically enriched salts IIIa or IVb and

iv) treating the diastereomerically enriched salts IIIa or IVb obtained in step ii) or step iii) with a base to liberate the enantiomerically enriched amines Ia or Ib.

Enantiomerically enriched (*S*)-(−)-3-*N*-methylamino-1-(2-thienyl)-1-propanol or (*R*)-(+)-3-*N*-methylamino-1-(2-thienyl)-1-propanol of the formulae Ia or Ib have an enantiomeric excess (e.e.) of >0%, preferably >50% and more preferably >70%.

The e.e. of (*S*)-(−)-3-*N*-methylamino-1-(2-thienyl)-1-propanol or (*R*)-(+)-3-*N*-methylamino-1-(2-thienyl)-1-propanol of the formulae Ia or Ib can be determined by chiral HPLC, for example.

An enantiomeric mixture of the amines Ia and Ib is either a racemic mixture of the amines Ia and Ib or a mixture, which is already enantiomerically enriched in Ia or Ib. Preferably the enantiomeric mixture of the amines Ia and Ib is a racemic mixture of Ia and Ib.

(−)-2,3:4,6-Di-*O*-isopropylidene-2-keto-L-gulonic acid or (+)-2,3:4,6-di-*O*-isopropylidene-2-keto-D-gulonic acid of the formulae IIa or IIb refer also to the hydrates of (−)-2,3:4,6-di-*O*-isopropylidene-2-keto-L-gulonic acid or (+)-2,3:4,6-di-*O*-isopropylidene-2-keto-D-gulonic acid.

Partially forming the diastereomeric salts of the formulae IIIa and IIIb or IVa and IVb means that the enantiomeric mixture of the amines Ia and Ib is treated with less than

1.0 mol equivalent of (−)-2,3:4,6-di-*O*-isopropylidene-2-keto-L-gulonic acid or (+)-2,3:4,6-di-*O*-isopropylidene-2-keto-D-gulonic acid in respect to said enantiomeric mixture so that only a part of said enantiomeric mixture is converted into the above diastereomeric salts, leaving the remainder of said enantiomeric mixture as free amines in the reaction mixture.

Completely forming the diastereomeric salts of the formulae IIIa and IIIb or IVa and IVb means that the enantiomeric mixture of the amines Ia and Ib is treated with at least 1.0 mol equivalent of (−)-2,3:4,6-di-*O*-isopropylidene-2-keto-L-gulonic acid or (+)-2,3:4,6-di-*O*-isopropylidene-2-keto-D-gulonic acid in respect to said enantiomeric mixture so that said enantiomeric mixture is completely (100%) converted into the above diastereomeric salts.

Preferably, the diastereomeric salts of the formulae IIIa and IIIb or IVa and IVb are partially or completely formed by treatment of an enantiomeric mixture of amines Ia and Ib with 0.4 to 1.1 mol equivalents of (−)-2,3:4,6-di-*O*-isopropylidene-2-keto-L-gulonic acid or (+)-2,3:4,6-di-*O*-isopropylidene-2-keto-D-gulonic acid in respect to said enantiomeric mixture.

More preferably, the diastereomeric salts of the formulae IIIa and IIIb or IVa and IVb are partially formed by treatment of an enantiomeric mixture of amines Ia and Ib with 0.4 to 0.6 mol equivalents of (−)-2,3:4,6-di-*O*-isopropylidene-2-keto-L-gulonic acid or (+)-2,3:4,6-di-*O*-isopropylidene-2-keto-D-gulonic acid in respect to said enantiomeric mixture.

Diastereomerically enriched salts IIIa or IVb liberate upon base treatment (*S*)-(−)-3-*N*-methylamino-1-(2-thienyl)-1-propanol or (*R*)-(+)-3-*N*-methylamino-1-(2-thienyl)-1-propanol of the formulae Ia or Ib having an e.e. of >0%, preferably >50% and more preferably >70%.

Diastereomerically enriched salts IIIa or IVb crystallize from the reaction mixture obtained in step i). When the diastereomeric salts IIIa and IIIb or IVa and IVb are partially formed, the crystallization of the diastereomerically enriched salts IIIa or IVb

removes more IIIa or IVb than IIIb or IVa from the solution and thus from the equilibrium of salt formation. As a consequence the equilibrium of salt formation is shifted towards the diastereomeric salts IIIa or IVb.

The diastereomerically enriched salts IIIa or IVb obtained in step ii) can be recrystallized. Preferably, the diastereomerically enriched salts IIIa or IVb are recrystallized to yield essentially diastereomerically pure salts IIIa or IVb, which upon base treatment liberate essentially enantiomerically pure amines Ia or Ib.

Essentially diastereomerically pure salts IIIa or IVb liberate upon base treatment (*S*)-(−)-3-*N*-methylamino-1-(2-thienyl)-1-propanol or (*R*)-(+)-3-*N*-methylamino-1-(2-thienyl)-1-propanol of the formulae Ia or Ib having an e.e. of >90%, preferably >95%.

Essentially enantiomerically pure (*S*)-(−)-3-*N*-methylamino-1-(2-thienyl)-1-propanol or (*R*)-(+)-3-*N*-methylamino-1-(2-thienyl)-1-propanol of the formulae Ia or Ib have an e.e. of >90%, preferably >95%.

The solvents used for the salt formation (step i), the crystallization (step ii) and the recrystallization (step iii) are identical or different and are selected from the group consisting of water, organic solvents, mixtures of water and at least one organic solvent and mixtures of an organic solvent and at least one other organic solvent.

The organic solvent is selected from the group consisting of C_{1-6}-alkanols, aliphatic ketones, aliphatic C_{2-6}-nitriles, nitro compounds, aliphatic amides, esters, carbon disulfide, tetramethylene sulfone, ethers, thioethers, halogenated hydrocarbons and hydrocarbons.

C_{1-6}-Alkanols can be branched or unbranched. Examples of C_{1-6}-alkanols are methanol, ethanol, propanol, 2-propanol (isopropanol), butanol, 2-methyl-1-propanol (isobutanol), 2-butanol, *tert*-butanol, pentanol, 3-methyl-1-butanol, 2-methyl-1-butanol, 2,2-dimethyl-1-propanol, 2-pentanol (*sec*-amylalcohol), 3-methyl-2-butanol, 2-methyl-2-butanol (*tert*-amylalcohol), 3-pentanol, hexanol, 2-hexanol, 3-hexanol, 3,3-dimethyl-1-butanol, 2-ethyl-1-butanol, 2-methyl-1-pentanol, 2-methyl-2-pentanol, 2-methyl-3-pentanol,

3-methyl-1-pentanol, 3-methyl-3-pentanol, 4-methyl-1-pentanol and 4-methyl-2-pentanol.

Aliphatic ketones can be ketones of the formula R^1R^2CO, wherein R^1 and R^2 are identical or different and are preferably aliphatic C_{1-4}-alkyl, which can be branched or unbranched. Examples of C_{1-4}-alkyl are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl and *tert*-butyl. Examples of ketones are acetone, 2-butanone (ethyl methyl ketone), 3-pentanone (diethyl ketone), 2-pentanone (methyl propyl ketone), 3-methyl-2-butanone (isopropyl methyl ketone), 2-hexanone (butyl methyl ketone), 3-hexanone (ethyl propyl ketone), 3,3-dimethyl-2-butanone (*tert*-butyl methyl ketone), 2-methyl-3-pentanone (ethyl isopropyl ketone) and 4-methyl-2-pentanone (isobutyl methyl ketone).

Aliphatic C_{2-6}-nitriles can be branched or unbranched. Examples of aliphatic C_{2-6}-nitriles are acetonitrile, propionitrile, butyronitrile, isobutyronitrile, valeronitrile, isovaleronitrile and hexanenitrile.

Nitro compounds can be aliphatic C_{1-6}-nitro compounds, which can be branched or unbranched, or aromatic nitro compounds, which can be substituted with methyl or ethyl. Examples of aliphatic C_{1-6}-nitro compounds are 1-nitromethane, 1-nitroethane, 1-nitropropane, 2-nitropropane, 1-nitrobutane, 2-methyl-2-nitropropane, 1-nitropentane and 2-nitrohexane. Examples of aromatic nitro compounds are nitrobenzene, 2-nitrotoluene and 3-nitrotoluene.

Aliphatic amides can be amides of the formula $R^3CO\text{-}NR^4R^5$, wherein R^3, R^4 and R^5 are identical or different and are preferably hydrogen, methyl or ethyl. Examples of amides are formamide, acetamide, *N*-methylformamide, *N*-methylacetamide, *N,N*-dimethylformamide, *N,N*-dimethylacetamide, *N*-ethylformamide, *N*-ethylacetamide and *N*-methylpropionamide.

Esters can be esters of the formula $R^6CO\text{-}OR^7$, wherein R^6 is hydrogen, C_{1-5}-alkyl, which can be branched or unbranched, aralkyl, or an aromatic residue, which is optionally substituted with C_{1-4}-alkyl, C_{1-4}-alkoxy or halogen, and R^7 is C_{1-5}-alkyl, which can be branched or unbranched, aralkyl or an aromatic residue. Examples of C_{1-4}-alkyl are given above. Examples of halogen are fluorine, chlorine, bromine and iodine. Examples of

C_{1-5}-alkyl are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl, *tert*-butyl, pentyl, isopentyl, 2-methyl-butyl, *sec*-pentyl, 2,2-dimethyl-propyl, 3-methyl-*sec*-butyl and 2-methyl-*sec*-butyl. Examples of aralkyl are benzyl and 2-phenylethyl. Example of aromatic residues are phenyl, 4-chlorophenyl and 4-tolyl. Examples of esters are methyl formate, ethyl formate, propyl formate, butyl formate, *tert*-butyl formate, isopentyl formate, phenyl formate, methyl acetate, ethyl acetate, propyl acetate, isopropyl acetate, butyl acetate, isobutyl acetate, *tert*-butyl acetate, pentyl acetate, isopentyl acetate, hexyl acetate, benzyl acetate, 2-phenylethyl acetate, phenyl acetate, methyl propionate, ethyl propionate, propyl propionate, *tert*-butyl propionate, methyl butyrate, ethyl butyrate, propyl butyrate, butyl butyrate, methyl valerate, ethyl valerate, pentyl valerate, methyl caproate, ethyl caproate, methyl phenylacetate, ethyl phenylacetate, methyl benzoate, ethyl benzoate, butyl benzoate, benzyl benzoate and phenyl benzoate.

Ethers can be either cyclic ethers or ethers of the formula R^8-O-R^9, wherein R^8 and R^9 are identical or different and are C_{1-4}-alkyl, which can be branched or unbranched, aralkyl, or an aromatic residue, which can be optionally substituted with methyl or ethyl. Examples of C_{1-4}-alkyl and aralkyl and an example of an aromatic residue are given above. Examples of an aromatic residue, which is substituted with methyl or ethyl, are 2-tolyl, 3-tolyl and 4-tolyl. Examples of cyclic ethers are tetrahydrofuran, tetrahydropyran and dioxane. Examples of ethers of the formula R^8-O-R^9 are diethyl ether, butyl methyl ether, *tert*-butyl methyl ether, *tert*-amyl methyl ether, butyl ethyl ether, *tert*-butyl ethyl ether, diisopropyl ether, dipropyl ether, anisole (methyl phenyl ether), 3-methyl-anisole, 4-methyl-anisole, benzyl methyl ether.

Thioethers can be either cyclic thioethers or thioethers of the formula R^{10}-S-R^{11}, wherein R^{10} and R^{11} are identical or different and are C_{1-4}-alkyl, which can be branched or unbranched, C_{2-3}-alkenyl or an aromatic residue, which can be optionally substituted with methyl or ethyl. Examples of C_{1-4}-alkyl and of aromatic residues are given above. Examples of C_{2-3}-alkenyl are vinyl and 2-propenyl (allyl).
Examples of cyclic thioethers are tetrahydrothiophene and pentamethylene sulfide. Examples of thioethers of the formula R^{10}-S-R^{11} are dimethyl sulfide, ethyl methyl sulfide, ethyl sulfide, *tert*-butyl methyl sulfide, isopropyl sulfide, propyl sulfide, butyl

sulfide, *sec*-butyl sulfide, allyl methyl sulfide, ethyl vinyl sulfide, thioanisole (methyl phenyl sulfide), ethyl phenyl sulfide and methyl 4-tolyl sulfide.

Halogenated hydrocarbons can be halogenated C_{1-4}-alkanes, which can be branched or unbranched, or halogenated aromatic hydrocarbons, which can be substituted with one or more C_{1-2}-alkyl. Examples of halogens are given above. The halogenated hydrocarbons can be substituted with one or more halogens, which can be identical or different. C_{1-2}-Alkyl is methyl or ethyl.
Examples of halogenated C_{1-4}-alkanes are dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, 1,2-dibromoethane, 1-bromo-2-chloroethane, 1-bromo-2-fluoroethane, 1,1-dichloropropane, 1,2-dichloropropane, 1,3-dichloropropane, 2,2-dichloropropane, 1,2-dibromopropane, 1,3-dibromopropane, 2,2-dibromopropane, 1-bromo-3-chloropropane, 1-bromo-3-fluoropropane, 1,2-dichlorobutane, 1,3-dichlorobutane, 1,4-dichlorobutane, 2,3-dichlorobutane, 1,2-dichloro-2-methylpropane, 1,2-dibromobutane, 1,3-dibromobutane, 2,3-dibromobutane, 1-bromo-4-chlorobutane and 1-bromo-3-chloro-2-methylpropane.
Examples of halogenated aromatic hydrocarbons are chlorobenzene, bromobenzene, 1,2-dichlorobenzene, 1,3-dichlorobenzene, 1,2-dibromobenzene, 1,3-dibromobenzene, 2-bromochlorobenzene, 1-bromo-2-fluorobenzene, 1-bromo-3-fluorobenzene, 1-bromo-4-fluorobenzene, 2-chlorotoluene, 3-chlorotoluene, 4-chlorotoluene, 2-bromotoluene, 3-bromotoluene, 2-chloro-*m*-xylene, 2-chloro-*p*-xylene, 4-chloro-*o*-xylene, (2-chloroethyl)benzene and 1-chloronaphthalene.

Hydrocarbons can be C_{5-8}-alkanes, which can be branched or unbranched, cyclic C_{5-8}-alkanes or aromatic hydrocarbons, which can be substituted with one or more C_{1-2}-alkyls. C_{1-2}-Alkyl is as defined above. Examples of C_{5-8}-alkanes are pentane, hexane, 2,2-dimethylbutane, 2,3-dimethylbutane, 2-methylpentane, 3-methylpentane, heptane, 2,2-dimethylpentane, 2,3-dimethylpentane, 2-methylhexane, 3-methylhexane, 2,2,2-trimethylbutane and octane. Examples of cyclic C_{5-8}-alkanes are cyclopentane, cyclohexane, cycloheptane and cyclooctane. Examples of aromatic hydrocarbons are benzene, toluene, *o*-xylene, *m*-xylene, *p*-xylene and ethylbenzene.

Preferably, the solvents used for the salt formation (step i), the crystallization (step ii) and the recrystallization (step iii) are identical or different and are polar solvents. The polar solvents are selected from the group of solvents consisting of water, a polar organic solvent, a mixture of water and at least one polar organic solvent and a mixture of a polar organic solvent and at least one other polar organic solvent.
The polar organic solvent is selected from the group consisting of C_{1-6}-alkanols, aliphatic ketones, aliphatic C_{2-6}-nitriles, nitro compounds, aliphatic amides and esters.

More preferably, the solvents used for the salt formation (step i), the crystallization (step ii) and the recrystallization (step iii) are identical or different and are selected from the group consisting of esters, C_{1-6}-alkanols and mixtures thereof.

Most preferably, the solvent used for the salt formation (step i), the crystallization (step ii) and the recrystallization (step iii) are identical or different and are ethanol or mixtures of ethanol and ethyl acetate.

Preferably, the salt formation (step i) is performed at a temperature between 20 and 120 °C, more preferably at a temperature between 40 and 100 °C. The temperature can change during the salt formation.

Preferably, the concentration of the enantiomeric mixture of amines Ia and Ib in the reaction mixture of the salt formation (step i) is between 2 and 20% (w/v), more preferably, between 2 and 15% (w/v).

The enantiomeric mixture of amines Ia and Ib and (−)-2,3:4,6-di-*O*-isopropylidene-2-keto-L-gulonic acid or (+)-2,3:4,6-di-*O*-isopropylidene-2-keto-D-gulonic acid can be added to the reaction vessel simultaneously or successively. Preferably, they are added successively. More preferably (−)-2,3:4,6-di-*O*-isopropylidene-2-keto-L-gulonic acid or (+)-2,3:4,6-di-*O*-isopropylidene-2-keto-D-gulonic acid are added to the enantiomeric mixture of amines Ia and Ib.

Diastereomerically enriched salts IIIa or IVb are crystallized from the reaction mixture obtained in step i). The diastereomerically enriched salts IIIa or IVb can be crystallized

directly from the reaction mixture obtained in step i) or after solvent exchange. The solvent exchange can be performed by partially or completely removing the solvent used in the salt formation (step i), e. g. by distillation, and simultaneously or successively adding another solvent. Preferably the diastereomerically enriched salts IIIa or IVb are crystallized directly from the reaction mixture obtained in step i). More preferably, the diastereomerically enriched salts IIIa or IVb are crystallized directly from the reaction mixture obtained in step i) upon cooling of the reaction mixture to a temperature from 0 to 15 °C. Most preferably, the diastereomerically enriched salts IIIa or IVb are crystallized directly from the reaction mixture obtained in step i) upon cooling of the reaction mixture to a temperature from 0 to 5 °C. The diastereomerically enriched salts IIIa or IVb are isolated e. g. by filtration or centrifugation.

The optional recrystallization of the diastereomerically enriched salts IIIa or IVb can be performed by dissolving said salts IIIa or IVb in the solvent, preferably at the reflux temperature of the solvent, and cooling the obtained mixture to a temperature from 0 to 15 °C, preferably to a temperature from 0 to 5 °C. The recrystallized diastereomerically enriched salts IIIa or IVb are isolated e. g. by filtration or centrifugation.

The isolated diastereomerically enriched salts IIIa or IVb obtained in step ii) or step iii) can be washed with a polar organic solvent. The polar organic solvent is as defined above. Preferably the polar organic solvent used for washing is selected from the group consisting of C_{1-6}-alkanols, esters and mixtures thereof. C_{1-6}-Alkanols and esters are as defined above.

The diastereomerically enriched salts IIIa or IVb obtained in step ii) or step iii) can be dissolved in a polar solvent and treated with a base, which is soluble in the polar solvent used, to liberate the enantiomerically enriched amines Ia or Ib. The polar solvent is as defined above. Preferably, the diastereomerically enriched salts IIIa or IVb obtained in step ii) or step iii) are dissolved in water and is treated with a water soluble inorganic or organic base. Examples of water soluble organic bases are trimethylamine, triethylamine, pyridine, 2-picoline, 3-picoline and 4-picoline. Examples of water soluble inorganic bases are lithium hydroxide, sodium hydroxide, potassium hydroxide, lithium carbonate, sodium carbonate, potassium carbonate, lithium hydrogen carbonate, potassium hydrogen

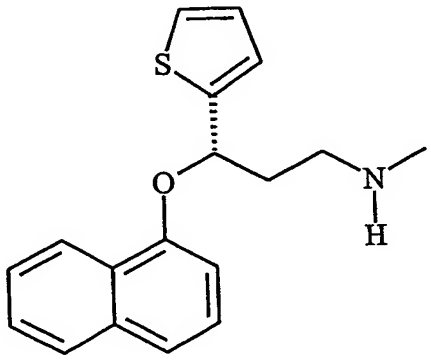
carbonate and ammonium hydroxide. Preferably, the base is a water soluble inorganic base. More preferably, the base is selected from the group consisting of sodium hydroxide, potassium hydroxide and sodium carbonate. The enantiomerically enriched amines Ia or Ib can be isolated e. g. by extraction with a suitable organic solvent. Examples of organic solvents suitable for extraction of the amines Ia or Ib are esters, ethers and halogenated hydrocarbons. Esters, Ethers and halogenated hydrocarbons are as defined above. Preferably, the solvent used for extracting the amines Ia or Ib is an ester or an ether. More preferably, the solvent used for extracting the amines Ia or Ib is ethyl acetate or *tert*-butyl methyl ether.

An enantiomeric mixture of the amines Ia and Ib can be prepared by reacting 2-acetyl-thiophene in a Mannich reaction with paraformaldehyde and methylamine hydrochloride to afford 3-*N*-methylamino-1-(2-thienyl)-1-propanone hydrochloride and subsequently reducing the latter with sodium borohydride to yield the racemic mixture of amines Ia and Ib. Preferably, the Mannich reaction is carried out using ethanol as solvent and under pressure at a temperature above the boiling point of ethanol, more preferably at a temperature from 100 to 120 °C. The reaction mixture obtained in the Mannich reaction can be employed directly in the reduction step. Alternatively, 3-*N*-methylamino-1-(2-thiophenyl)-1-propanone can be isolated from the reaction mixture obtained in the Mannich reaction, e.g. by crystallization, and can be employed, after optional recrystallization, in the reduction step. Examples of solvents suitable for recrystallizing 3-*N*-methylamino-1-(2-thienyl)-1-propanone hydrochloride are C_{1-6}-alkanols, preferably isopropanol. C_{1-6}-Alkanols are as defined above. Preferably, the reduction of 3-*N*-methylamino-1-(2-thienyl)-1-propanone with sodium borohydride is performed in ethanol at a temperature from 0 to 10 °C, more preferably at a temperature from 4 to 6 °C. The isolated racemic mixture of amines Ia and Ib can be optionally further purified by distillation under reduced pressure.

(–)-2,3:4,6-Di-*O*-isopropylidene-2-keto-L-gulonic acid is commercially available. Alternatively, it can be prepared by oxidation of 2,3:4,5-di-*O*-isopropylidene-L-sorbose, e. g. electrochemically (DE 2410034), or by diacetalization of 2-keto-L-gulonic acid, e. g. by treatment with 2,2-dimethoxypropane (US 6,239,293 B1).

(+)-2,3:4,6-Di-*O*-isopropylidene-2-keto-D-gulonic acid can be prepared analogously starting from 2,3:4,5-di-*O*-isopropylidene-D-sorbose or from 2-keto-D-gulonic acid.

The process of the present invention for the preparation of enantiomerically enriched (*S*)-(+)-methyl-[3-(1-naphthyloxy)-3-(2-thienyl)-propyl]-amine (duloxetine) of the formula

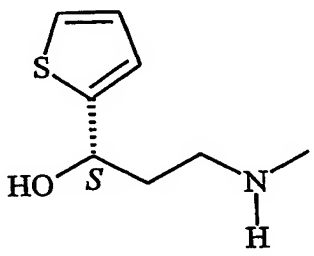


(Va)

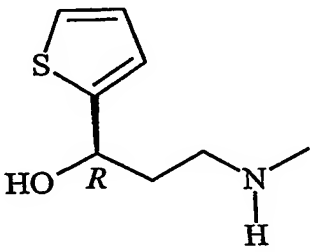
or a pharmaceutically acceptable salt thereof

comprises the steps of

i) reacting an enantiomeric mixture of (*S*)-(−)-3-*N*-methylamino-1-(2-thienyl)-1-propanol and (*R*)-(+)-3-*N*-methylamino-1-(2-thienyl)-1-propanol of the formulae

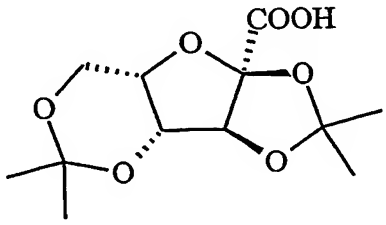


(Ia) and



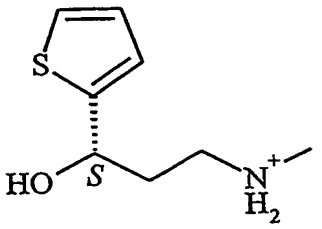
(Ib)

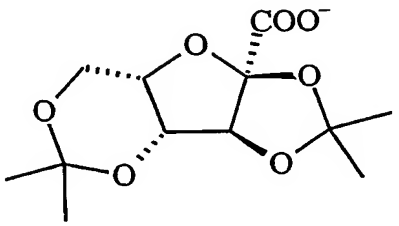
with (−)-2,3:4,6-di-*O*-isopropylidene-2-keto-L-gulonic acid of the formula



(IIa)

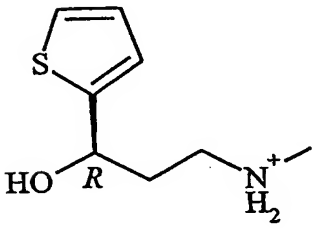
to partially or completely form the diastereomeric salts of the formulae

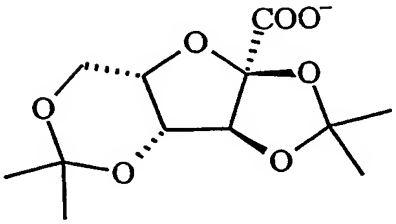




(IIIa)

and





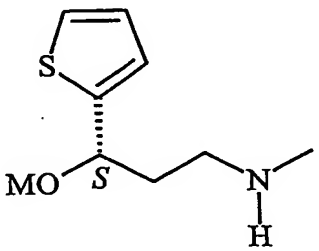
(IIIb)

ii) crystallizing the diastereomerically enriched salt IIIa from the reaction mixture obtained in step i),

iii) optionally recrystallizing said diastereomerically enriched salt IIIa,

iv) treating the diastereomerically enriched salt IIIa obtained in step ii) or step iii) with a base to liberate the enantiomerically enriched amine Ia,

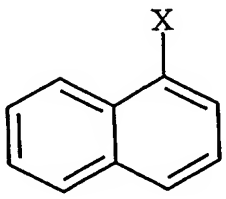
v) converting the enantiomerically enriched amine Ia to the corresponding enantiomerically enriched alkoxide of the formula



(VIa)

wherein M is a monovalent metal,

vi) reacting said enantiomerically enriched alkoxide VIa with a 1-halonaphthalene of the formula



(VII)

wherein X is halogen, to yield enantiomerically enriched duloxetine (Va), and

vii) optionally treating said duloxetine (Va) with an acid to form a pharmaceutical acceptable salt thereof.

All definitions given for the process for the preparation of enantiomerically enriched amines Ia or Ib apply, when appropriate, accordingly to this process.

Enantiomerically enriched duloxetine (Va) has an e.e. of >0%, preferably >50% and more preferably >70%.

Pharmaceutically acceptable salts of duloxetine are acid addition salts of duloxetine formed by treatment of duloxetine (VIa) with an inorganic or organic acid. Examples of inorganic acids are hydrochloric acid, hydrobromic acid, hydriodic acid, sulfuric acid, phosphoric acid and carbonic acid. Examples of organic acids are formic acid, acetic acid, malonic acid, succinic acid, maleic acid, fumaric acid, oxalic acid, citric acid, tartaric acid, benzoic acid, *p*-toluenesulfonic acid and methanesulfonic acid. Examples of pharmaceutically acceptable salts of duloxetine are (*S*)-(+)-methyl-[3-(1-naphthyloxy)-3-(2-thienyl)-propyl]-ammonium chloride, bromide, iodide, hydrogensulfate, sulfate, hydrogensulfite, sulfite, phosphate, hydrogenphosphate, dihydrogenphosphate, formate, citrate, malonate, succinate, maleate, fumarate, oxalate, citrate, tartrate, benzoate, *p*-toluenesulfonate and methanesulfonate.

The enantiomerically enriched alkoxideVIa has an e.e. of >0%, preferably >50% and more preferably >70%.

The enantiomerically enriched amine Ia is converted to the enantiomerically enriched alkoxide VIa, wherein M is a monovalent metal. Preferably, M is an alkali metal selected from the group consisting of lithium, sodium and potassium. Examples of alkoxides of the formula VIa are lithium (*S*)-(−)-3-*N*-methylamino-1-(2-thienyl)-1-propoxide, sodium (*S*)-(−)-3-*N*-methylamino-1-(2-thienyl)-1-propoxide and potassium (*S*)-(−)-3-*N*-methylamino-1-(2-thienyl)-1-propoxide. The enantiomerically enriched amine Ia can be converted to the enantiomerically enriched alkoxide VIa by treatment of said amine Ia with an alkali metal selected from the group of lithium, sodium and potassium, or by treatment of amine Ia with a suitable base. Examples of suitable bases are lithium hydride, lithium *N*,*N*-diisopropylamide, sodium hydride, sodium *tert*-butoxide, potassium hydride and potassium *tert*-butoxide.

The enantiomerically enriched alkoxide VIa reacts with 1-halonaphtalene of the formula VII to yield enantiomerically enriched duloxetine (Va). The halogen of 1-halonaphthalene of the formula VII is selected from the group consisting of fluorine, chlorine, bromine and iodine. Preferably, 1-halonaphtalene is 1-fluoronapthalene.

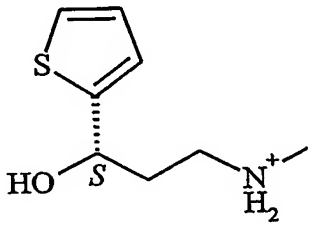
The diastereomerically enriched salt IIIa obtained in step ii) is preferably recrystallized to yield essentially diastereomerically pure salt IIIa, which upon base treatment liberates essentially enantiomerically pure amine Ia, which is converted to essentially enantiomerically pure alkoxide VIa, which reacts with 1-halonaphthalene to yield essentially enantiomerically pure duloxetine (Va).

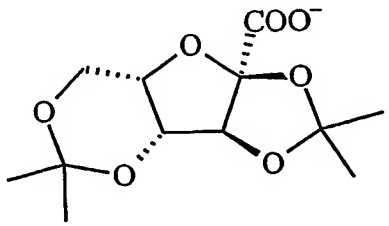
The essentially enantiomerically pure alkoxide VIa has an e.e. of >90%, preferably >95%.

Essentially enantiomerically pure duloxetine (Va) has an e.e. of >90%, preferably >95%.

The following compounds are also part of the invention:

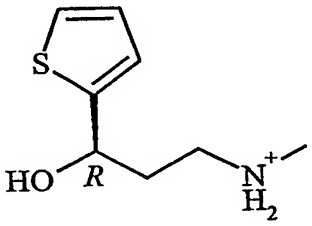
(*S*)-3-*N*-Methylammonio-1-(2-thienyl)-1-propanol 2,3:4,6-di-*O*-isopropylidene-2-keto-L-gulonate of the formula

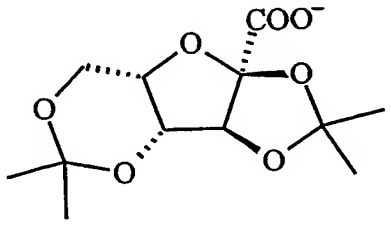




(IIIa)

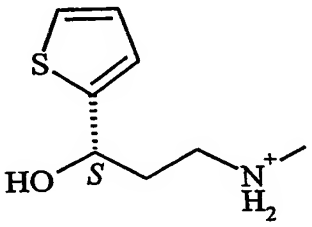
(*R*)-3-*N*-Methylammonio-1-(2-thienyl)-1-propanol 2,3:4,6-di-*O*-isopropylidene-2-keto-L-gulonate of the formula

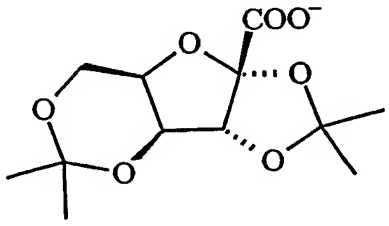




(IIIb)

(*S*)-3-*N*-Methylammonio-1-(2-thienyl)-1-propanol 2,3:4,6-di-*O*-isopropylidene-2-keto-D-gulonate of the formula

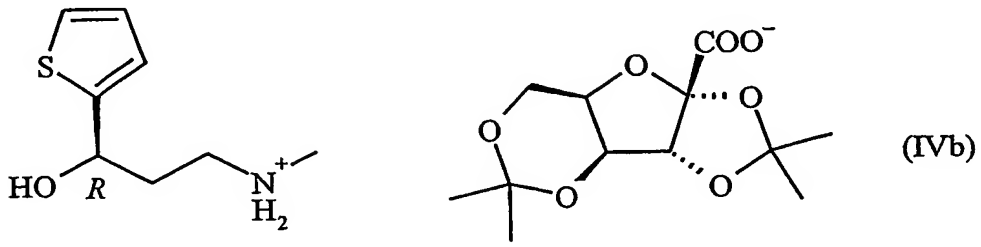




(IVa)

and

(*R*)-3-*N*-Methylammonio-1-(2-thienyl)-1-propanol 2,3:4,6-di-*O*-isopropylidene-2-keto-D-gulonate of the formula



(IVb)

Example 1

Preparation of 3-*N*-methylamino-1-(2-thienyl)-1-propanone hydrochloride

A mixture of 2-acetylthiophene (25.5 g, 200 mmol), methylamine hydrochloride (14.9 g, 220 mmol), paraformaldehyde (8.2 g, 280 mmol) and ethanol (100 mL) was heated in an autoclave at 110 °C for 9 h. The obtained light brown solution was cooled to 20 °C and part of the ethanol (50 mL) was removed by distillation under vacuum. Ethyl acetate (200 mL) was added to the residue to afford a thick suspension, which was cooled to 0 °C and kept for 45 min at that temperature. The obtained precipitate was isolated by filtration and dried yielding 3-*N*-methylamino-1-(2-thienyl)-1-propanone hydrochloride (29.3 g, 71%) as a slightly yellow powder.

Example 2

Preparation of (±)-3-*N*-methylamino-1-(2-thienyl)-1-propanol

Sodium hydroxide (4.0 g of a 50% aqueous solution) was added to a mixture of 3-*N*-methylamino-1-(2-thienyl)-1-propanone hydrochloride (10.3 g, 50 mmol) and ethanol (35 mL) at 4 °C in about 5 min. Neat sodium borohydride (0.95 g, 25 mmol) was added in several portions in about 30 min to afford a beige suspension which was stirred at 4 °C for additional 4 h. Acetone (10 mL) was added dropwise in 5 min and the mixture

was stirred for additional 10 min before water (20 mL) was added. The mixture was concentrated about 5 times under vacuum and the obtained residue was extracted with *tert*-butyl methyl ether (2 × 20 mL). The collected organic phases were concentrated under vacuum affording (±)-3-*N*-methylamino-1-(2-thienyl)-1-propanol (7.2 g, 84%) as an orange oil which crystallized spontaneously after a few h. ^{1}H-NMR (DMSO-d_6, 400 MHz): 7.35 (1 H, dd, J = 4.8, 1.0), 6.94 (1 H, dd, J = 4.8, 3.6), 6.90 (1 H, dd, J = 3.6, 1.0), 4.90 (1 H, t), 3.7 (2 H, m), 2.56 (2 H, m), 2.25 (3 H, s), 1.79 (2 H, q); ^{13}C-NMR (DMSO-d_6): 150.9, 126.3, 123.7, 122.3, 67.8, 48.5, 38.7, 36.0.

Example 3

Analytical hydrolysis of (*S*)-3-*N*-methylammonio-1-(2-thienyl)-1-propanol 2,3:4,6-di-*O*-isopropylidene-2-keto-L-gulonate to (*S*)-(−)-3-*N*-methylamino-1-(2-thienyl)-1-propanol

Sodium hydroxide (0.3 g of a 30% aqueous solution) was added to a solution of (*S*)-3-*N*-methylammonio-1-(2-thienyl)-1-propanol 2,3:4,6-di-*O*-isopropylidene-2-keto-L-gulonate (0.50 g, 1.08 mmol) in water (10 mL). *tert*-Butyl methyl ether (10 mL) was added. The two phases were separated and the aqueous one was extracted with *tert*-butyl methyl ether (2 × 10 mL). The collected organic phases were dried over sodium sulfate, filtrated and concentrated to yield a colorless oil which crystallized spontaneously affording (*S*)-(−)-3-*N*-methylamino-1-(2-thienyl)-1-propanol as a white solid. The e.e. of the product was determined by chiral HPLC.

Example 4

Preparation of (*S*)-(−)-3-*N*-methylamino-1-(2-thienyl)-1-propanol using 1 mol equivalent of (−)-2,3:4,6-di-*O*-isopropylidene-2-keto-L-gulonic acid

4.1. Salt formation and crystallization

(±)-3-*N*-Methylamino-1-(2-thiophenyl)-1-propanol (8.6 g, 50 mmol) was dissolved in ethyl acetate (150 mL) and the obtained solution was heated to reflux. In a separate vessel, (−)-2,3:4,6-di-*O*-isopropylidene-2-keto-L-gulonic acid (14.6 g, 50 mmol) was dissolved in ethanol (100 mL) and the solution was added in about 15 min to the amine

solution. Afterwards, the mixture was heated to reflux for 40 min and then cooled to 0 °C. The obtained precipitate was filtrated, washed with ethyl acetate (2 × 50 mL) and dried for 15 h at 50 °C and 25 mbar affording (*S*)-3-*N*-methylammonio-1-(2-thienyl)-1-propanol 2,3:4,6-di-*O*-isopropylidene-2-keto-L-gulonate as a white solid (10.7 g, 45%). A sample was hydrolyzed as described in example 3 affording (*S*)-(−)-3-*N*-methylamino-1-(2-thienyl)-1-propanol having an e.e. of 80 to 85% as determined by chiral HPLC.

4.2 Recrystallization

(*S*)-3-*N*-Methylammonio-1-(2-thienyl)-1-propanol 2,3:4,6-di-*O*-isopropylidene-2-keto-L-gulonate (30.0 g, 64 mmol) and ethanol (450 mL) was in ethanol (450 mL) at reflux temperature. The solution was cooled to 20 °C in 2 h and filtered. The obtained precipitate was washed with ethyl acetate (40 mL) and dried at 40 to 50 °C and 25 mbar affording (*S*)-3-*N*-methylammonio-1-(2-thienyl)-1-propanol 2,3:4,6-di-*O*-isopropylidene-2-keto-L-gulonate (81%). A sample was hydrolyzed as described in example 3 affording (*S*)-(−)-3-*N*-methylamino-1-(2-thienyl)-1-propanol having an e.e. of 96 to 97% as determined by chiral HPLC.

4.3. Hydrolysis

4.3.1. Hydrolysis by treatment with potassium hydroxide

Potassium hydroxide (3.6 g of a 50% aqueous solution) was added to a solution of (*S*)-3-*N*-methylammonio-1-(2-thienyl)-1-propanol 2,3:4,6-di-*O*-isopropylidene-2-keto-L-gulonate (5.0 g, 10.8 mmol) in water (15 mL). *tert*-Butyl methyl ether (35 mL) was added. The two phases were separated and the aqueous one was extracted with *tert*-butyl methyl ether (14 mL). The collected organic phases were washed with water (12 mL), dried over sodium sulfate, filtrated and concentrated to yield a colorless oil which crystallized spontaneously affording (*S*)-(−)-3-*N*-methylamino-1-(2-thienyl)-1-propanol as a white solid (1.30 g, 70%) having an e.e. of 96 to 97% as determined by chiral HPLC.

4.3.2. Hydrolysis by treatment with sodium carbonate

Sodium carbonate (1.82 g, 17.3 mmol) was added to a solution of (*S*)-3-*N*-methylammonio-1-(2-thienyl)-1-propanol 2,3:4,6-di-*O*-isopropylidene-2-keto-L-gulonate (8.0 g, 17.3 mmol) in water (45 mL). The mixture was stirred for 15 min and extracted with ethyl acetate (4 × 20 mL). The collected organic phases were dried over sodium sulfate,

filtrated and concentrated to yield a colorless oil which crystallized spontaneously affording (*S*)-(−)-3-*N*-methylamino-1-(2-thienyl)-1-propanol as a white solid (1.8 g, 61%) having an e.e. of 96 to 97% as determined by chiral HPLC.

Example 5

Preparation of (*S*)-(−)-3-*N*-methylamino-1-(2-thienyl)-1-propanol using 0.6 mol equivalents of (−)-2,3:4,6-di-*O*-isopropylidene-2-keto-L-gulonic acid

5.1. Salt formation and crystallization

(±)-3-*N*-Methylamino-1-(2-thiophenyl)-1-propanol (3.4 g, 20 mmol) was dissolved in ethyl acetate (28 mL) and the obtained solution was heated to reflux. In a separate vessel, (−)-2,3:4,6-di-*O*-isopropylidene-2-keto-L-gulonic acid (3.5 g, 12 mmol) was dissolved in ethanol (10 mL) and the solution was added in about 15 min to the amine solution. Afterwards, additional ethyl acetate (25 mL) was added and the mixture was heated to reflux for 10 h, then cooled to 0 °C. The suspension was stirred at 0 °C for 1 h. The obtained precipitate was filtrated, washed with ethyl acetate (10 mL) and dried for 15 h at 50 °C and 25 mbar affording (*S*)-3-*N*-methylammonio-1-(2-thienyl)-1-propanol 2,3:4,6-di-*O*-isopropylidene-2-keto-L-gulonate as a white solid (3.7 g, 40%). A sample was hydrolyzed as described in example 3 affording (*S*)-(−)-3-*N*-methylamino-1-(2-thienyl)-1-propanol having an e.e. of 79% as determined by chiral HPLC.

5.2. Recrystallization

(*S*)-3-*N*-Methylammonio-1-(2-thienyl)-1-propanol 2,3:4,6-di-*O*-isopropylidene-2-keto-L-gulonate (0.45 g, 1 mmol) was dissolved in ethanol (4 mL) at reflux temperature. The mixture was cooled to 0 °C. The obtained precipitate was filtered, washed with *tert*-butyl methyl ether (1 mL) and dried at 40 to 50 °C and 25 mbar affording (*S*)-3-*N*-methylammonio-1-(2-thienyl)-1-propanol 2,3:4,6-di-*O*-isopropylidene-2-keto-L-gulonate (0.30 g, 66%). A sample was hydrolyzed as described in example 3 affording (*S*)-(−)-3-*N*-methylamino-1-(2-thienyl)-1-propanol having an e.e. of 96 to 97% as determined by chiral HPLC.

Example 6

Preparation of (*S*)-(−)-3-*N*-methylamino-1-(2-thienyl)-1-propanol using 0.5 mol equivalents of (−)-2,3:4,6-di-*O*-isopropylidene-2-keto-L-gulonic acid

6.1. Salt formation and crystallization

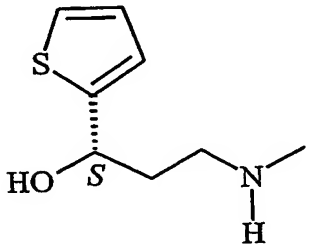
(±)-3-*N*-Methylamino-1-(2-thienyl)-1-propanol (3.4 g, 20 mmol) was dissolved in ethyl acetate (28 mL) and the obtained solution was heated to reflux. In a separate vessel, (−)-2,3:4,6-di-*O*-isopropylidene-2-keto-L-gulonic acid (2.9 g, 10 mmol) was dissolved in ethanol (28 mL) and the solution was added in about 15 min to the amine solution. Afterwards, additional ethyl acetate (100 mL) was added and the mixture was heated to reflux for 30 min, then cooled to 0 °C. The suspension was stirred at 0 °C for 1 h. The obtained precipitate was filtrated and dried for 15 h at 50 °C and 25 mbar affording (*S*)-3-*N*-methylammonio-1-(2-thienyl)-1-propanol 2,3:4,6-di-*O*-isopropylidene-2-keto-L-gulonate as a white solid (2.9 g, 31%). A sample was hydrolyzed as described in example 3 affording (S)-(−)-3-*N*-methylamino-1-(2-thienyl)-1-propanol having an e.e. of 75% as determined by chiral HPLC.

5.2. Recrystallization

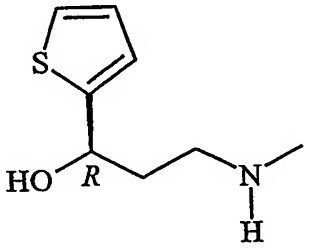
(*S*)-3-*N*-Methylammonio-1-(2-thienyl)-1-propanol 2,3:4,6-di-*O*-isopropylidene-2-keto-L-gulonate (4.0 g, 8.7 mmol) was dissolved in ethanol (56 mL) at reflux temperature. The mixture was cooled to room temperature. The obtained precipitate was filtered, washed with *tert*-butyl methyl ether (5 mL) and dried at 40 to 50 °C and 25 mbar affording (*S*)-3-*N*-methylammonio-1-(2-thienyl)-1-propanol 2,3:4,6-di-*O*-isopropylidene-2-keto-L-gulonate (2.9 g, 73%). A sample was hydrolyzed as described in example 3 affording (*S*)-(−)-3-*N*-methylamino-1-(2-thienyl)-1-propanol having an e.e. of 95 to 96% as determined by chiral HPLC.

Claims

1. Process for the preparation of enantiomerically enriched (*S*)-(−)-3-*N*-methylamino-1-(2-thienyl)-1-propanol or (*R*)-(+)-3-*N*-methylamino-1-(2-thienyl)-1-propanol of the formulae

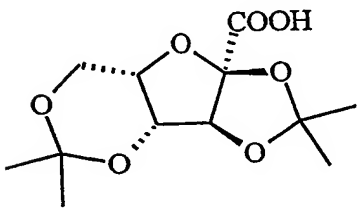

(Ia)

or

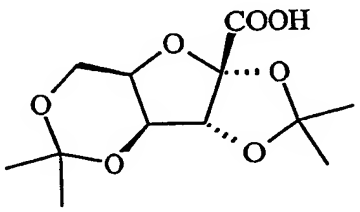

(Ib)

comprising the steps of

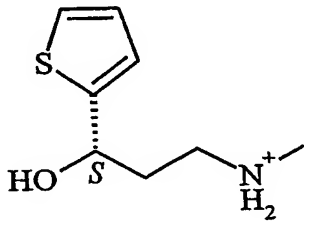
i) treating an enantiomeric mixture of the amines Ia and Ib with (−)-2,3:4,6-di-*O*-isopropylidene-2-keto-L-gulonic acid or (+)-2,3:4,6-di-*O*-isopropylidene-2-keto-D-gulonic acid of the formulae


(IIa)

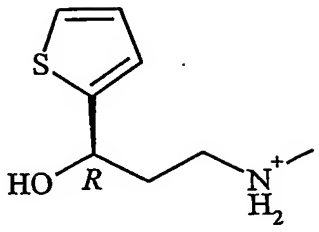
or

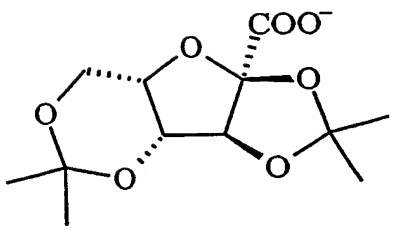

(IIb)

to partially or completely form the diastereomeric salts of the formulae


(IIIa)

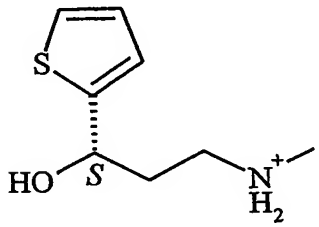
and

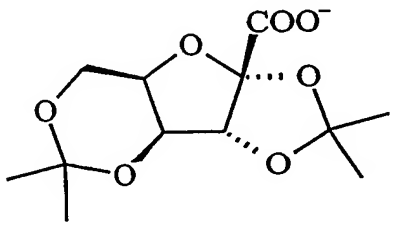




(IIIb)

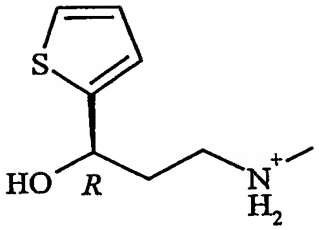
or the diastereomeric salts of the formulae

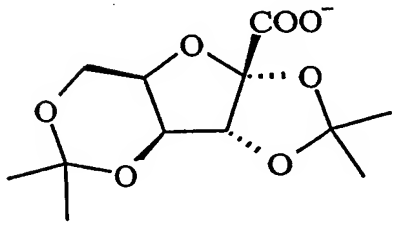




(IVa)

and





(IVb)

ii) crystallizing the diastereomerically enriched salts IIIa or IVb from the reaction mixture obtained in step i),

iii) optionally recrystallizing said diastereomerically enriched salts IIIa or IVb, and

iv) treating the diastereomerically enriched salts IIIa or IVb obtained in step ii) or step iii) with a base to liberate the enantiomerically enriched amines Ia or Ib.

2. Process of claim 1 wherein the diastereomerically enriched salts IIIa or IVb obtained in step ii) are recrystallized to yield essentially diastereomerically pure salts IIIa or IVb, which upon base treatment liberate essentially enantiomerically pure amines Ia or Ib.

3. Process of claim 1 or 2 wherein the solvents used for the salt formation (step i), the crystallization (step ii) and the recrystallization (step iii) are identical or different and are polar solvents.

4. Process of claim 3 wherein the solvents are selected from the group consisting of esters, C_{1-6}-alkanols and mixtures thereof.

5. Process of claim 4 wherein the solvents are ethanol or mixtures of ethanol and ethyl acetate.

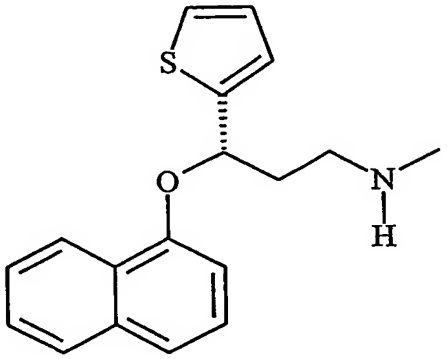
6. Process of one of the claims 1 to 5 wherein 0.4 to 1.1 mol equivalents (−)-2,3:4,6-di-*O*-isopropylidene-2-keto-L-gulonic acid of the formula IIa or (+)-2,3:4,6-di-*O*-isopropylidene-2-keto-D-gulonic acid of the formula IIb in respect to the enantiomeric mixture of amines Ia and Ib are used.

7. Process of claim 6 wherein 0.4 to 0.6 mol equivalents (−)-2,3:4,6-di-*O*-isopropylidene-2-keto-L-gulonic acid of the formula IIa or (+)-2,3:4,6-di-*O*-isopropylidene-2-keto-D-gulonic acid of the formula IIb in respect to the enantiomeric mixture of amines Ia and Ib are used.

8. Process of one of the claims 1 to 7 wherein the base is a water soluble inorganic base.

9. Process of claim 8 wherein the base is selected from the group consisting of sodium hydroxide, potassium hydroxide and sodium carbonate.

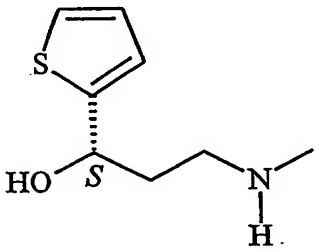
10. Process for the preparation of enantiomerically enriched (*S*)-(+)-methyl-[3-(1-naphthyloxy)-3-(2-thienyl)-propyl]-amine (duloxetine) of the formula



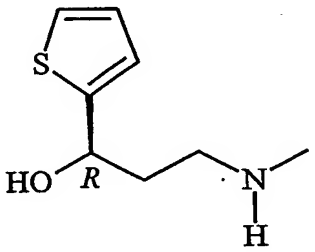
(Va)

or a pharmaceutically acceptable salt thereof, comprising the steps of

i) reacting an enantiomeric mixture of (*S*)-(−)-3-*N*-methylamino-1-(2-thienyl)-1-propanol and (*R*)-(+)-3-*N*-methylamino-1-(2-thienyl)-1-propanol of the formulae

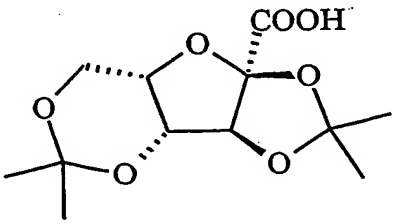


(Ia) and



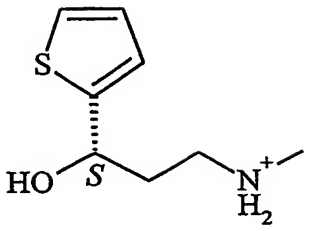
(Ib)

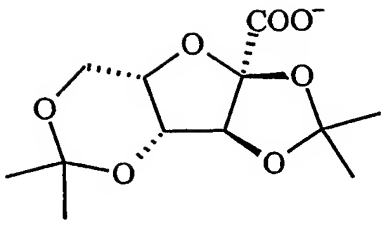
with (−)-2,3:4,6-di-*O*-isopropylidene-2-keto-L-gulonic acid of the formula



(IIa)

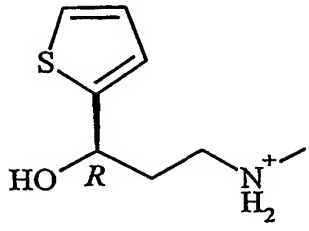
to partially or completely form the diastereomeric salts of the formulae

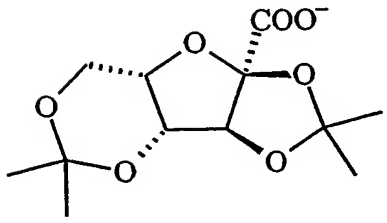




(IIIa)

and





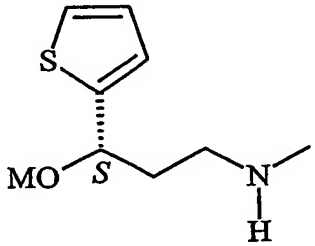
(IIIb)

ii) crystallizing the diastereomerically enriched salt IIIa from the reaction mixture obtained in step i),

iii) optionally recrystallizing said diastereomerically enriched salt IIIa,

iv) treating the diastereomerically enriched salt IIIa obtained in step ii) or step iii) with a base to liberate the enantiomerically enriched amine Ia,

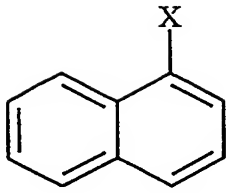
v) converting the enantiomerically enriched amine Ia to the corresponding enantiomerically enriched alkoxide of the formula



(VIa)

wherein M is a monovalent metall,

vi) reacting said enantiomerically enriched alkoxide VIa with a 1-halonaphthalene of the formula



(VII)

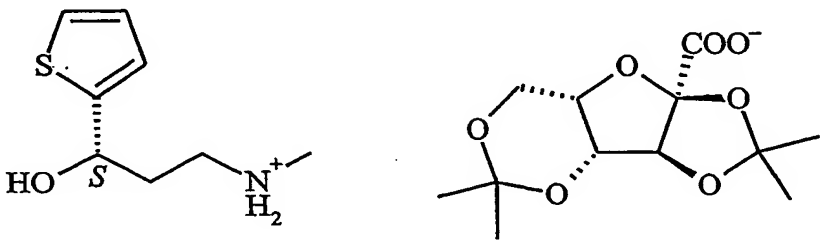
wherein X is halogen, to yield enantiomerically enriched duloxetine (Va), and optionally

vii) treating said duloxetine (Va) with an acid to form a pharmaceutical acceptable salt thereof.

11. Process of claim 10 wherein the diastereomerically enriched salt IIIa obtained in step ii) is recrystallized to yield essentially diastereomerically pure salt IIIa, which upon base treatment liberates essentially enantiomerically pure amine Ia, which is converted to essentially enantiomerically pure alkoxide VIa, which reacts with 1-halonaphthalene to yield essentially enantiomerically pure duloxetine Va.

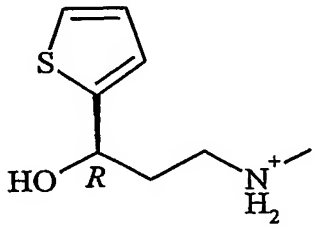
12. Process of claims 10 or 11 wherein the 1-halonaphthalene is 1-fluoronaphthalene.

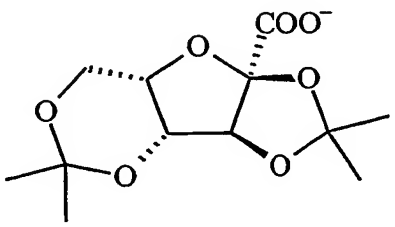
13. (*S*)-3-*N*-Methylammonio-1-(2-thienyl)-1-propanol 2,3:4,6-di-*O*-isopropylidene-2-keto-L-gulonate of the formula



(IIIa)

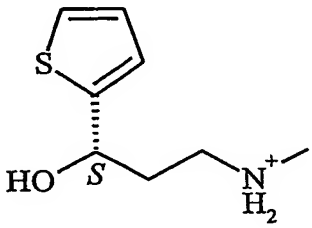
14. (*R*)-3-*N*-Methylammonio-1-(2-thienyl)-1-propanol 2,3:4,6-di-*O*-isopropylidene-2-keto-L-gulonate of the formula

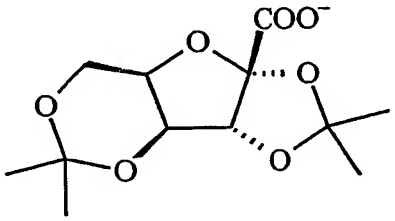




(IIIb)

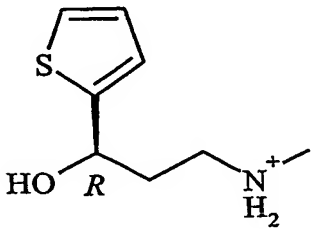
15. (*S*)-3-*N*-Methylammonio-1-(2-thienyl)-1-propanol 2,3:4,6-di-*O*-isopropylidene-2-keto-D-gulonate of the formula

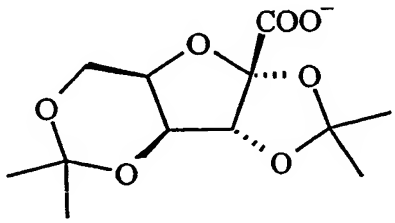




(IVa)

16. (*R*)-3-*N*-Methylammonio-1-(2-thienyl)-1-propanol 2,3:4,6-di-*O*-isopropylidene-2-keto-D-gulonate of the formula





(IVb)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/07312

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07H9/04 C07D333/20 C07D493/14 //(C07D493/14,319:00, 317:00,317:00,307:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07H C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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